REMARKS

In light of the Examiner vacating the Office Action mailed June 11, 2003 in the Office Action mailed August 1, 2003, this paper and these remarks are only directed at the Office Action mailed August 1, 2003.

In the Specification:

Applicants have amended the specification to correct a typographical error. In the paragraph beginning on page 148, line 11, "deposit" has been amended to be grammatically correct by making it plural, "deposits." No new matter has been introduced to the specification by this amendment.

Applicants have also amended the specification on page 148, line 15, to assure that all restrictions imposed by the depositor on the availability to the public of the deposited material will be irrevocably removed upon the granting of the pertinent U.S. patent. No new matter has been introduced to the specification by this amendment.

In the Claims:

Claims 22-26 have been amended to clarify that the claimed variant or fragment polypeptides all have the characteristic of being encoded by a nucleic acid that is amplified in lung or colon tumors, as well as a certain percentage of sequence similarity to the amino acid sequence of PRO357. Support for amendment to claims 22-26 may be found at pages 119-137 of the specification.

New claims 35 and 36 have been added. New claims 35 and 36 do not encompass new matter. Support for new claims 35 and 36 may be found at pages 59-62 of the specification.

Oath/Declaration:

The Examiner has objected to the oath or declaration of the present application under 37 C.F.R. § 1.52(c) because there are non-initialed and/or non-dated alterations.

Specifically, there are changes to the address of the inventor Dan L. Eaton that are neither initialed nor dated. To correct this error, Applicants herein submit a new declaration, *see* Appendix A, properly executed by Dan L. Eaton, which, pursuant to 37 C.F.R. § 1.67(a) (2) (*See also* MPEP § 602.03 (8th ed. 2001)), remedies the defective oath. Therefore, Applicants respectfully request that this rejection be withdrawn.

Claim Rejections:

35 U.S.C. § 101 - Utility

The Examiner rejected claims 22-34 alleging that they are not supported by either a substantial asserted utility or a well established utility. The Examiner notes that the claims are directed to polypeptides having 80-100% sequence identity to SEQ ID NOS: 68 or 69. Further, the Examiner notes that the specification discloses that the mRNA levels of SEQ ID NO:68 are increased in tumors but the Examiner contends that the specification does not disclose whether the protein of SEQ ID NO:69 is expressed at any increased level. Thus, the Examiner asserts that an increased copy number of DNA does not provide a readily apparent use for the polypeptide, when there is no information regarding level of expression, activity or role in cancer. The Examiner supports his contention by citing Pennica *et al*, *PNAS* 95:14717-14722, 1998, which the Examiner alleges provides an example where gene copy number is amplified but RNA expression is reduced. In concluding his rejection, the Examiner specifically alleges that the specification does not teach an increase in the expressed polypeptide of SEQ ID NO:69, nor does it disclose a correlation between any specific disorder and an altered level or form of the claimed polypeptides, nor does it predict whether the claimed polypeptides would be overexpressed or underexpressed in a specific, diseased tissue compared to the healthy tissue control.

Applicants respectfully disagree with the Examiner's assertion that claims 22-34 are not supported by either a substantial asserted utility or a well established utility. The substantial asserted and well-established diagnostic utility of PRO357 is supported at pages 119-137 of the instant specification.

More specifically, Example 28, the gene amplification experiment, discussed at pages 119-137, demonstrates, using measurements in ΔCt values (one ΔCt unit is defined as corresponding to 1 PCR cycle or approximately a 2-fold amplification relative to normal) that the nucleic acid encoding PRO357 is amplified in lung and colon tumors. This data supports a diagnostic utility for nucleic acids, polypeptides and antibodies to PRO357.

For further explanation of the significance of the PRO357 ΔCt values set forth in Table 10, beginning on page 127 of the instant specification, Applicants respectfully direct the Examiner's attention to the enclosed Declaration of Audrey D. Goddard, Ph.D. (*see* Appendix B, "the Goddard Declaration"), an expert in the field of cancer biology and an inventor of the present invention. The Goddard Declaration makes it clear that skilled artisans recognize a substantial utility for the claimed invention at the time of filing. Specifically, the Goddard Declaration illustrates the acceptance in the art of gene amplification data as an indicator of cancerous tissue. For example, in paragraph 7, Dr. Goddard specifically asserts her opinion that:

> [a]n at least 2-fold increase in gene copy number in a tumor tissue sample relative to a normal (*i.e.*, non-tumor) sample is significant and useful in that the detected increase in gene copy number in the tumor sample relative to the normal sample serves as a basis for using relative gene copy number . . . as a diagnostic marker for the presence or absence of tumor in a tissue sample of unknown pathology.

The pending claims are directed to polypeptides encoded by a nucleic acid sequence that is amplified in lung or colon tumors. The specification specifically asserts a utility for these polypeptides. For example, see page 137, lines 24-25, stating that "polypeptides encoded by the DNAs tested have utility as diagnostic markers for determining the presence of tumor cells in lung and/or colon tissue samples." Thus, Applicants maintain that claims 22-34 are supported by an asserted substantial utility as well as a well established utility.

Specifically, the data present in Example 28 resulted from experiments using appropriate controls for aneuploidy (see, for example, page 137, lines 13-16). Applicants used framework mapping to control for aneuploidy and to ensure that the observed ΔCt value represents relevant gene amplification. Thus, the reported data are an indication of relevant gene amplification, and support the conclusion that PRO357, and related proteins and antibodies, can be used as a cancer diagnostic. Furthermore, considering the aneuploidy controls used by Applicants, a skilled artisan would not be required to undertake undue experimentation to practice the claimed invention.

An Applicant's assertion of utility creates a presumption of utility that will be sufficient to satisfy the utility requirement of 35 U.S.C. § 101, "unless there is a reason for one skilled in the art to question the objective truth of the statement of utility or its scope." *In re Langer*, 503 F.2d 1380, 1391, 183 USPQ 288, 297 (CCPA 1974). *See also In re Jolles*, 638 F.2d 1322, 206 USPQ 885 (CCPA 1980); *In re Irons*, 340 F.2d 974, 144 USPQ 351 (9165); *In re Sichert*, 566 F.2d 1154, 1159, 196 USPQ 209, 212-213 (CCPA 1977).

Compliance with 35 U.S.C. § 101 is a question of fact. *Raytheon v. Roper*, 724 F.2d 951, 956, 220 USPQ 592, 596 (Fed. Cir. 1983) *cert. denied*, 469 U.S. 835 (1984). The evidentiary standard to be used throughout *ex parte* examination in setting forth a rejection is a preponderance of the totality of the evidence under consideration. *In re Oetiker*, 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992). Thus, to overcome the presumption of truth that an assertion of utility by the Applicant enjoys, the Examiner must establish that it is more likely than not that one of ordinary skill in the art would doubt the truth of the statement of utility. Only after the Examiner made a proper *prima facie* showing of lack of utility, shifts the burden of rebuttal to the Applicant. The issue will then be decided on the totality of the evidence.

In the present case a *prima facie* case of lack of utility has not been established. First, one basis for the Examiner's conclusion of lack of utility is based on a quote from Pennica *et al*, cited in the Goddard Declaration, which is filed with this response and discussed above. Based on this reference, the Examiner correctly concludes that increased copy number does not *necessarily* result in increased protein expression. The standard, however, is not absolute certainty. The fact that in the case of a specific class of closely related molecules there seemed to be no correlation between gene amplification and the level of mRNA/protein expression, does not establish that it is more likely than not, in general, that such correlation does not exist. The Examiner has not shown whether the lack of correlation observed for the family of polypeptides referenced in Pennica *et al.* is typical, or is merely a discrepancy, an exception to the rule of correlation. Indeed, the working hypothesis among those skilled in the art is that,

if a gene is amplified in cancer, the encoded protein is likely to be expressed at an elevated level.

However, even if a *prima facie* case of lack of utility had been established, it should be withdrawn on consideration of the totality of the evidence. Specifically, even if one assumes arguendo that it is more likely than not that there is no correlation between gene amplification and increased mRNA/protein expression, a polypeptide encoded by a gene that is amplified in cancer would still have a specific and substantial utility.

Enclosed herein is a second declaration. This second declaration is made by Avi Ashkenazi, Ph.D. (*see* Appendix C), also an expert in the field of cancer biology and an inventor of the present invention. As Dr. Ashkenazi explains:

> Even when amplification of a cancer marker gene does not result in significant over-expression of the corresponding gene product, this very absence of gene product over-expression of the corresponding gene product still provides significant information for cancer diagnosis and treatment. Thus, if over-expression of the gene product does not parallel gene amplification in certain tumor types but does so in others, then parallel monitoring of gene amplification and gene product over-expression enables more accurate tumor classification and hence better determination of suitable therapy. In addition, absence of over-expression is crucial information for the practicing clinician. If a gene is amplified but the corresponding gene product is not over-expressed, the clinician accordingly will decide not to treat a patient with agents that target that gene product.

Accordingly, the PRO357 polypeptide has a substantial, specific utility, and Applicants respectfully request that the Examiner withdraw the present rejection.

Applicants do note that the Examiner cites a series of references (Tischer et al. US Pat. No. 5,194,596; Benjamin et al. Development 125:1591-1598, 1998; Vukicevic et al. PNAS 93:9021-9026, 1996; Massague, Cell 49: 437-438, 1987; PIlbeam et al. Bone 14:717-720, 1993; Kopchick et al. US Pat. No. 5,350,836) in support of his contention that the application's disclosure that PRO357 functions as known insulin growth factors is not credible because of numerous examples in the literature of polypeptide families whose members have distinct biological activities. In further support of this position, the Examiner contends that the art acknowledges that function cannot be predicted based

solely on structural similarity. However, the utility of the present invention is supported by the gene amplification assay discussed in Example 28 of the application, demonstrating that PRO357 is encoded by a nucleic acid that is amplified in lung and colon tumors. In order to satisfy the utility requirement of 35 U.S.C. § 101, Applicants need only provide one credible assertion of specific and substantial utility for each claimed invention. The credibility of the asserted utility is to be assessed from the perspective of one of ordinary skill in the art in view of the disclosure and any other evidence of record (e.g., test data, affidavits or declarations from experts in the art, patents or printed publications) that is probative of Applicants' assertions. MPEP § 2107-II(B)(ii) (8th ed. 2001).

In view of these remarks, Applicants respectfully assert that the claimed invention has utility and is fully enabled. Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw the rejection of claims 22-34 under 35 U.S.C. § 101.

35 U.S.C. § 112 ¶ 1, Enablement-Utility

The Examiner has rejected claims 22-34 under 35 U.S.C. § 112 ¶1, alleging that because the claimed invention is not supported by either a specific asserted utility or a well established utility, one skilled in the art would not know how to use the claimed invention. As discussed in the remarks above, addressing the rejection under 35 U.S.C. § 101 for lack of utility, Applicants respectfully submit that the claimed polypeptide has the specific, substantial, and credible diagnostic utility as demonstrated in the gene amplification experiments discussed in Example 28 at pages 119-137 of the application.

Applicants respectfully request the Examiner reconsider and withdraw the rejection of claims 22-34 under 35 U.S.C. § 112 ¶1 for their alleged inadequate disclosure on how to use the claimed invention.

35 U.S.C. § 112 ¶, Indefiniteness

The Examiner rejects claims 22-27, 30-31, 33-34 under 35 U.S.C. § 112 ¶2, alleging that these claims are indefinite. Specifically, the Examiner contends that the disclosed

polypeptide, PRO357, is soluble and not disclosed as being expressed on the cell surface. Thus, the Examiner contends the limitation that the claimed protein comprises an extracellular domain is indefinite because the art does not recognize soluble proteins as having "extracellular domains."

Applicants respectfully submit that PRO357 is not a soluble protein.

First, as shown in Figure 26, PRO 357 has multiple features which indicate that it is a membrane localized, non-soluble protein. For example, PRO357 has a transmembrane domain, consisting of amino acids 501-522, indicating that PRO357 spans a biological membrane; *i.e.*, it is a membrane-localized protein, containing both intra- and extra-cellular domains.

Second, the presence of three N-glycosylation sites in the PRO357 amino acid sequence further argues against PRO357 being soluble. N-linked glycosylation typically modifies membrane and secreted proteins and most soluble proteins are not glycosylated. (*See e.g.*, R. Gupta and S. Brunak, Prediction of Glycosylation Across the Human Proteome and the Correlation to Protein Function, Pacific Symposium on Biocomputing 2002: 310-322; Appendix B).

Applicants maintain that a skilled artisan can conclude from the PRO357 sequence data that the protein is not soluble. However, even if PRO357 *were* a soluble protein, Applicants respectfully submit that the claims are still not indefinite because the art recognizes that a soluble protein may, for a time, be on the cell surface. It is well established in the art that soluble polypeptides often first exist as transmembrane polypeptides and are then processed by membrane-bound peptidases to their soluble form. *See e.g.,* Sunthornthepvarakul *et al.,* J Clin Endocrinol Metab. 1999 Oct;84(10):3792-6; Alberts *et al.,* Molecular Biology of the Cell, p. 557 (3d eds., Garland, New York, 1994) (Appendix D).

The Examiner also states that "if the protein had an extracellular domain, the recitation of 'the extracellular domain' . . . 'lacking its associated signal sequence' (claim 22, part (d), for example) is indefinite as a signal sequence is not generally considered to be part of an extracellular domain, as signal sequences are cleaved from said domains in the process of secretion from the cell." Applicants respectfully disagree, pointing out that, as taught by the Alberts *et al.* textbook, Molecular Biology of the Cell, 3rd edition, (pp. 557-560; Appendix D), a signal sequence is not necessarily cleaved from the extracellular domain of a protein: a "signal peptide is often (but not always) removed from the finished protein...." *Id.* For example, in polypeptides with both signal sequences and distant transmembrane domains, the polypeptide can exist as a transmembrane polypeptide with its signal sequence uncleaved. The signal sequence is later cleaved with the transmembrane domain influencing the cleavage process. *See e.g.,* Rehm et al., EMBO J. 7:1573-1582 (April 2, 2001) (Appendix D). Depending on further processing of the polypeptide can either later be released as a soluble polypeptide or remain a transmembrane polypeptide. Thus, Applicants respectfully submit that the art *does* recognize that a signal sequence can be part of an extracellular domain.

Accordingly, Applicants respectfully request that the rejections of claims 22-27, 30-31, 33-34 under 35 U.S.C. § 112 ¶2 for indefiniteness be withdrawn.

35 U.S.C. § 112 ¶ 1, Written Description

The Examiner has rejected claims 22-26 and 33-34 under 35 U.S.C. § 112, first paragraph, contending that they contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicants respectfully disagree with the Examiner's statement that the written description requirement has not been satisfied. As the Examiner notes, the written description requirement requires that an applicant's specification convey with

reasonable clarity to those skilled in the art, that as of the filing date sought, he or she was in possession of the invention. *Vas-Cath, Inc. v. Mahurkar,* 19 USPQ2d 1111, 1116 (Fed. Cir. 1991). A written description of an invention involving a chemical genus requires a precise definition, such as by structure, formula . . . of the claimed subject matter ***sufficient to distinguish it from other materials***. *Univ. of Calif. v. Eli Lilly & Co.,* 43 USPQ2d 1398, 1405 (Fed. Cir. 1997) (emphasis added). Since one skilled in the art can distinguish a described formula from other formulas and therefore can ***identify many of the species*** that the claims encompass, a described formula is normally an adequate description of the claimed invention. *Id.* at 1406 (emphasis supplied). Moreover, as noted in the Guidelines for Examination of Patent Applications Under 35 U.S.C. § 112, First Paragraph, "Written Description" Requirement ("the Guidelines"), there is a "***strong presumption***" that an adequate written description of the claimed invention is present when the application is filed and, consequently, rejection of an original claim for lack of written description "***should be rare***." 66(4) *Fed. Reg.* 1099, 1105 (2001); *see also*, *In re Wertheim*, 191 USPQ 90, 97 (CCPA 1976). The Guidelines further state that "[t]he examiner has the initial burden of presenting by a preponderance of evidence why a person skilled in the art would not recognize in an applicant's disclosure a description of the invention defined by the claims." 66(4) *Fed. Reg.* at 1107; 191 USPQ at 97, (emphasis supplied).

Compliance with the written description requirement does not require an applicant to describe exactly the subject matter claimed; rather, the description must clearly allow a person of ordinary skill in the art to recognize that he or she invented what is claimed. *Vas-Cath Inc. v. Mahurkar*, 19 USPQ2d 1111, 1116 (Fed. Cir. 1991). The test is whether the originally filed specification reasonably conveys to a person having ordinary skill in the art that applicant had possession of the subject matter later claimed. *In re Kaslow*, 217 USPQ 1089 (Fed. Cir. 1991). Moreover, in order to have possession of members of a claimed genus, the specification ***need not*** describe all of the species that the genus encompasses. *Amgen Inc. v. Chugai Pharmaceutical Co.*, 18 USPQ2d 1016, 1027 (Fed. Cir. 1991).

In view of the legal standard regarding the written description requirement under 35 U.S.C. § 112, first paragraph, in combination with the interpretation of the written description requirement by the United States Patent and Trademark Office as set forth in the Guidelines, Applicants respectfully submit that the instant specification satisfies the written description requirement because it would be clear to one of skill in the art that Applicants possessed the claimed subject matter at the time of filing the instant application.

For example, several structural features, such as open reading frames, the translation initiation site, and predicted polypeptide precursors of the cDNA sequence of PRO357, are disclosed at lines 14-20 on page 107 of the specification. A host of PRO357 features disclosed in Figure 26 describe the polypeptide in great detail. For example, some of the PRO357 features described are conserved structures forming different protein domains: signal sequences; the transmembrane domain; N-glycosylation sites; a tyrosine kinase phosphorylation site; an N-myristoylation site; a prokaryotic membrane lipoprotein lipid attachment site; an EGF-like domain cysteine pattern signature; and a leucine zipper pattern (Figure 26). A skilled artisan would easily recognize start and stop codons, leucine rich repeats, a relationship to the acid labile subunit (ALS) of insulin-like growth factor, and other signatures and homologies of the non-coding regions of the DNA44804-1248 encoding the PRO357 polypeptide. Some of these features are further disclosed at p. 58, lines 4-12 of the application.

The Examiner also alleges that the claims are drawn to a genus of inoperative polynucleotides that is defined only by sequence identity, and that the instant specification does not describe any biological activity, expression pattern, phenotype, disease or condition, ligand, binding partner or any other specific feature that is associated with PRO357.

Applicants have amended claims 22-26 to clarify that the claimed variant and fragment polypeptides encompassed by claims 22-26 have the characteristic of being encoded by a nucleic acid that is amplified in lung and colon tumors. Moreover, Applicants respectfully

disagree that the specification fails to describe any biological activity, expression pattern, phenotype, disease or condition, ligand, or binding partner. In fact, at page 145, lines 11-20, the specification discloses expression patterns associated with PRO357, including tissues where PRO357 nucleic acids are significantly expressed and tissues where they are not. As exemplified in the data presented in Table 10 on p. 125-127, the nucleic acid encoding PRO357 is amplified in lung and colon tumors. The specification also discloses disease conditions associated with PRO357 overexpression, including at page 137, lines 11-26, describing that significant amplification of the PRO357 nucleic acid in lung and colon tumors is suggestive of PRO357's role in tumor formation and growth. Thus, the claimed genus is not defined only by sequence identity.

Claims 22-26 are directed to isolated nucleic acids that are overexpressed in lung and colon tumors and have at least 80%, 85%, 90%, 95%, and 99% sequence identity to (a) the amino acid sequence of the polypeptide shown in Figure 26 (SEQ ID NO:69); (b) the amino acid sequence of the polypeptide shown in Figure 26 (SEQ ID NO:69), lacking its associate signal peptide; (c) the amino acid sequence encoding the extracellular domain of the polypeptide shown in Figure 26 (SEQ ID NO:69); (d) the amino acid sequence encoding the extracellular domain of the polypeptide shown in Figure 26 (SEQ ID NO:69), lacking it associated signal peptide; (e) the amino acid sequence of the polypeptide encoded by the full-length coding sequence of the cDNA deposited under ATCC accession number 209527 As such, claims 22-26 require that (1) the nucleic acids encompassed within the claims not have substantial variation from the disclosed species that is actually reduced to practice in the specification (*i.e.*, SEQ ID NO: 69) in that they must possess at least 80%, 85%, 90%, 95%, or 99% sequence identity to SEQ ID NO:69 or to the nucleic acid encoding the polypeptide of SEQ ID NO:69 and (2) that the nucleic acids encompassed within the claim must possess the specified biological functionality (*i.e.*, be encoded by a nucleic acid that is amplified in lung and colon tumors), a biological function that is exhibited by the nucleic acid of SEQ ID NO:68.

The analysis for determining whether the present specification provides written description support for the invention defined by claims 22-26, 33-34 may be performed by numerous methods, several of which are described in the Guidelines and further exemplified in the Revised Interim Written Description Guidelines Training Materials ("Written Description Training Materials"), published on the USPTO website at http://www.uspto.gov/web/offices/pac/writtendesc.pdf (a complete copy of which is enclosed herewith as Appendix E). These Written Description Training Materials are designed to provide additional clarity to the Guidelines which are published in the Federal Register, Volume 66, No. 4, pages 1099-1111. In fact, as indicated in the USPTO press release of March 1, 2000 introducing the Written Description Examination Training Materials (Press Release #00-15), these training materials were promulgated by the USPTO and are:

> "designed to aid PTO's patent examiners in applying the interim written description and utility guidelines in a uniform and consistent manner to promote the issuance of high quality patents. The training materials will also assist patent applicants in responding to the PTO when utility or written description issues are raised during the examination of a patent application." (emphasis added)

With regard to claims 22-26, 33-34, the present situation is analogous to Example 14 on pages 53-55 of the Written Description Training Materials (Appendix E). More specifically, in Example 14 on pages 53-55 of the enclosed Written Description Training Materials, a claim directed to a protein and variants thereof having 95% sequence identity, all of which share the same biological function, is analyzed for its compliance with the written description requirement of 35 U.S.C. § 112, first paragraph. The Written Description Training Materials conclude that such a claim satisfies the written description requirement of 35 U.S.C. § 112, first paragraph, when (1) a single protein sequence is actually reduced to practice, (2) procedures for making variants of that "reduced to practice" protein sequence are conventional in the art, and (3) an assay is described which allows identification of other proteins having the same biological activity. The reasoning provided by the USPTO in the Written Description Training Materials is that:

> "[t]here is actual reduction to practice of the single disclosed species. The specification indicates that the genus of proteins that must be variants of SEQ ID

> NO:...does not have substantial variation since all of the variants must possess the specified [biological function] and must have at least 95% identity to the reference sequence, SEQ ID NO:...The single species disclosed ***is representative of the genus*** because all members have at least 95% structural identity with the reference compound and because of the presence of an assay which applicant provided for identifying all of the at least 95% identical variants of SEQ ID NO:...which are capable of the specified [biological function]. One of skill in the art would conclude that applicant was in possession of the necessary common attributes possessed by members of the genus.....{As such], the disclosure meets the requirements of 35 U.S.C. § 112, first paragraph, as providing adequate written description for the claimed invention." (Appendix E at pages 54-55) (emphasis added).

Analogous to Example 14 of the Written Description Training Materials, the present specification discloses and actually reduces to practice a polypeptide recited in claims 22-6, 33-34 (*i.e.*, SEQ ID NO:69) as well as a nucleic acid encoding that polypeptide (*i.e.*, SEQ ID NO:68). Moreover, the polypeptide variants encompassed within claims 22-26, 33-34 ***do not have substantial variation*** with SEQ ID NO:69 because (a) they share at least 80%, 85%, 90%, 95% or 99% sequence identity with SEQ ID NO:69 or the nucleic acid encoding the polypeptide sequence of SEQ ID NO:69. (Applicants note that methods for routinely determining nucleic acid and/or amino acid sequence identity are described in detail in the present specification at page 23, line 34 to page 29, line 2, *see also* pages 34-54), and (b) they share the biological function of being encoded by a nucleic acid that is amplified in lung and colon tumors. (Applicants note that the specification describes in detail in Example 28 and on page 69, lines 1-15, routine assays which are useful for identifying nucleic acids encoding polypeptides having these biological functions). As such, the polypeptides encompassed within claims 22-26 and 33-34 all share substantial common structural features (*i.e.*, 80%, 85%, 90%, 95%, or 99% sequence identity) and substantial common functional features (*i.e.,* being encoded by a nucleic acid that is amplified in lung and colon tumors). Moreover, the present specification also describes conventionally known methods used and known in

the art for preparing a multitude of polypeptide variants (see the present specification at page 59, line 13 to page 63, line 36).

Given the above, Applicants respectfully submit that claims 22-26, 33-34 satisfy the written description requirement of 35 U.S.C. § 112, first paragraph because the specification provides "a precise definition, such as by structure, formula ... of the claimed subject matter *sufficient to distinguish it from other materials*" as required by the Federal Circuit in *Univ. of California v. Eli Lilly and Co.*, 43 USPQ2d 1398 (Fed. Cir. 1997). Moreover, claims 22-26 are analogous to the claim found to satisfy the written description requirement in Example 14 of the enclosed Written Description Training Materials. As such, under the Guidelines and the examination training materials promulgated by the USPTO for ensuring consistent examination of written description compliance during prosecution of patent applications, Applicants respectfully submit that the written description requirement of 35 U.S.C. § 112, first paragraph, is satisfied for claims 22-26, 33-34. Therefore, Applicants respectfully request this ground of rejection be withdrawn.

35 U.S.C. § 112 ¶ 1, Enablement- Deposit

The Examiner rejected claims 22-27 and 32-34 under 35 U.S.C. § 112, first paragraph, as failing to provide an enabling disclosure, stating that the specification lacks complete deposit information. More specifically, the Examiner states that it is not clear that the cDNA deposited under ATCC accession No. 209527 is known and publicly available or can be reproducibly isolated from nature without undue experimentation, nor whether it is the same as SEQ ID NO:68 or contains sequences in addition to SEQ ID NO:68.

The deposit of the biological material was made under the provisions of the Budapest Treaty. Further, Applicants have amended the specification to incorporate the requisite assurance, under the Budapest Treaty, that "all restrictions imposed by the depositor on the availability to the public of the deposited material will be irrevocably removed upon the granting of the pertinent U.S. patent." No new matter has been added by this amendment to the specification.

At page 148, line 5, the material indicated as DNA44804-1248 is shown as being deposited with the American Type Culture Collection, under ATCC Dep. No. 209527. At page 107, lines 10-17, the material indicated as DNA44804-1248 is described as the full-length DNA sequence for PRO357. As indicated at p. 107, line 13, the entire nucleotide sequence of clone DNA44804-1248 is shown in Figure 25 (SEQ ID NO:68). It is clear that the deposit ATCC 209527 corresponds to the disclosed SEQ ID NO:68.

Applicants respectfully request that this ground of rejection be withdrawn.

35 U.S.C. § 112 ¶ 1 - Enablement

The Examiner has further rejected claims 22-34 under 35 U.S.C. § 112 ¶1 for lack of enablement. As the Examiner notes, the factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is undue include: 1) the nature of the invention, 2) the state of the prior art, 3) the relative skill of those in the art, 4) the level of predictability in the art, 5)

the existence of working examples, 6) the breadth of the claims, 7) the amount of direction or guidance by the inventor, and 8) the quantity of experimentation needed to make or use the invention. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400,1404 (Fed. Cir. 1988).

First, the nature of the invention is that of a well defined class of polypeptides, each having the characteristic of being encoded by a nucleic acid that is amplified in lung and colon tumors, in addition to being at least 80% identical to the disclosed wild type polypeptide.

The Examiner, however, contends that such claims are not enabled. First, the Examiner alleges that there is no functional limitation in the claims as far as the polypeptide. Next, although the Examiner notes that Applicants have taught the polypeptide consisting of the extracellular domain or the mature form of SEQ ID NO:69, as well as the putative signal sequence, the Examiner contends that one would not know if a polypeptide with the claimed homology would function as a polypeptide of SEQ ID NO:69. Finally, the Examiner contends that the function of PRO357 is undisclosed.

Applicants respectfully disagree. First, as noted above, Applicants have amended claims 22-26 to clarify that the claimed polypeptides are encoded by a nucleic acid that is amplified in lung and colon tumors. Second, as discussed previously, one of ordinary skill in the art would recognize that the polypeptides encoded by the PRO357 DNA, which was determined to be amplified in the gene amplification experiment discussed in Example 28 on pages 119-137 of the specification, would function as diagnostic markers for determining the presence of tumor cells in lung and/or colon tissue samples. *See* Appendix B, Appendix C. Moreover, even if the amplification of PRO357 polypeptides did not follow the amplification pattern of the nucleic acid encoding PRO357, the skilled artisan would still recognize that such an expression pattern would function in more accurately classifying a tumor with this unique expression pattern. In addition, as Dr. Ashkenazi declares, if a gene is amplified but the corresponding gene product is not over-expressed, that expression pattern functions to alert a clinician that

she should not employ a treatment that utilizes agents that target the gene product. *See* Appendix B. Thus, Applicants respectfully submit that they have disclosed several functions of the claimed PRO357 polypeptides. Further, one of skill in the art would be able to determine whether a polypeptide with the claimed homology functions as a polypeptide of SEQ ID NO:69.

Second and third, the state of the prior art and the relative skill of those in the art, are advanced. However, the Examiner contends that the claims encompass an unreasonable number of inoperative polypeptides which one skilled in the art would not know how to use. For example, the Examiner cites a series of references in support of the contention that even a single amino acid change can have dramatic and unpredictable effects on a protein's function. (Burgess et al. J. Cell Biol. 111:2129-2138, 1990; Lazar et al. MCB 8L1247-1252, 1988; Lin et al. Biochemistry 14:1559-1563, 1975).

While Applicants agree with the Examiner and the cited references that, on occasion, even a single modification or substitution in a protein sequence can alter protein function, one of skill in the art would recognize that many polypeptides have conserved amino acids, or active sites and it is modifications affecting these conserved amino acids that can result in altered protein function. *See* Lewin, "Genes VII" at Parts 1-4, Oxford University Press, 2000.

Applicants further submit that one of skill in the art will also recognize that there are numerous nucleic acids, encoding *non-conserved* amino acids that could be changed in a sequence without substantially altering the structure, physiological function, or activity of the polypeptide. Even further, one of skill in the art would also recognize that even some conserved amino acids can be substituted without significant adverse effect upon the function of the polypeptide because even extensively changing the amino acid or nucleic acid sequence may still result in polypeptides that retain many epitopes unique to the wild type polypeptide.

At page 61 (Table 6 and accompanying text) of the instant specification, Applicants suggest several methods for substituting amino acids in various sequences, while still conserving the structure and function of the encoded wild-type polypeptide, its transmembrane localization, binding properties, *etc.* For instance, using site-directed mutagenesis, PCR mutagenesis, and other techniques described at pages 61-62, a practitioner in the art would be able to introduce desired conservative or non-conservative amino acid substitutions, yet maintain PRO357 functionality.

Even further, amended claims 22-26 require that the variant or fragment polypeptides within their scope be encoded by a nucleic acid that is amplified in lung or colon tumors. Therefore, the skilled artisan would recognize that variants and fragments of PRO357 would have the same or at least similar utility to full length polypeptides in detecting, monitoring or preparing treatments for various cancers.

Fourth, the art is predictable as evidenced by the references and declarations discussed herein.

Fifth, as the Examiner notes, Applicants have disclosed, as SEQ ID NO:69, an example of the wild type of the polypeptide that is claimed. Moreover, contrary to the Examiner's assertion that the skilled artisan would not know how to use non-identical polypeptides, because all non-identical polypeptides are required to have the same characteristic of being encoded by a nucleic acid that is amplified in lung and colon tumors, one of skill in the art would know how to use such non-identical polypeptides.

Sixth, the amended claims are not broad because they require the claimed class of polypeptides to have the same characteristic and a high percentage of sequence identity.

Seventh, Applicant Inventors have provided a significant amount of guidance in the specification, as well as in the attached declarations. For example, the Examiner argues that there is much evidence that protein levels do not always correlate with

steady-state mRNA levels or alterations in mRNA levels. Dr. Ashkenazi, an inventor on this application, clarifies, in paragraph 6 of his declaration, that the skilled artisan would recognize that:

> . . . even when amplification of a cancer marker gene does not result in significant over-expression of the corresponding gene product, this very absence of gene product over-expression still provides significant information for cancer diagnosis and treatment.

Appendix C. Moreover, gene amplification in cancer is a special situation in which there is a very high correlation between gene amplification and protein over-expression. *See* Appendix F (G. Brodeur & M. Hogarty, Gene Amplification in Human Cancer: Biological and Clinical Significance, 161-172, B. Vogelstein & K. Kinzler eds, McGraw-Hill, New York, 1998).

Even further, one of the references cited by the Examiner, Fu et al., does not demonstrate amplification of the p53 gene and therefore is not an apt system with which to compare Applicants' disclosure. Specifically, gene amplification is a mechanism of activation of oncogenes and p53 is a tumor suppressor gene. In fact, the protein level of p53 is controlled, in part, by the protein MDM2 whose gene is amplified in many tumor systems with associated increases in MDM2 protein and decreases in p53 protein levels. (*See* Appendix F, Sherr, Cancer Res. 60: 3689-95, 2000; Momand et al., Nuc. Acids Res. 26, 3453-3459, 1998).

Finally, some degree of routine experimentation might possibly be necessary to perform the substitutions of nucleotides and determine the functionality of the modified PRO357-based polypeptides. However, even a "considerable amount of experimentation is permissible, if it is merely routine, or if the specification provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed." *In re Wands*, 858 F. 2d 731, 737 (Fed. Cir. 1988). According to the MPEP § 2164.01, "the fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation."

Considering the "Wands" factors, one skilled in the art would not have to undertake undue experimentation to make and use the invention specified by claims 22-34. *See, In re Wands*, 858 F.2d 731, 737, 8 U.S.P.Q.2d 1400, 1404 (Fed. Cir. 1988). Accordingly, Applicants respectfully request that the rejections of claims 22-34 be withdrawn.

SUMMARY

Applicants believe that currently pending claims 22-36 are patentable. Applicants respectfully request the Examiner grant early allowance of this application. The Examiner is invited to contact the undersigned attorneys for Applicants via telephone if such communication would expedite this application.

Respectfully submitted,

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